Methylmercury: A Story of Loaves and Fishes

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Mercury

Mercury is naturally present in the environment. It is part of the composition of the earth's crust and may be found in air, water, soil, aquatic sediments, and in living plants and animals. It occurs in several chemical forms, including both inorganic and organic mercury compounds.

All forms of mercury may be neurotoxic. There are considerable data to suggest that methylmercury (MeHg) is highly neurotoxic, especially at high exposure levels. The fetus is especially vulnerable to its neurotoxic effects at doses too low to show postnatal effects. Less data are available regarding the potential human neurotoxicity of other forms of mercury. This paper will review the status of our knowledge regarding exposure to MeHg.

Human Environmental Exposure to Methylmercury

Around 70 percent of the mercury in the environment comes from anthropogenic sources, primarily emissions from coal-fired electric power generation facilities and waste dumps (Mason, et al., 1994) although natural sources such as volcanos and mines also deposit it in the environment (Fitzgerald & Clarkson, 1991). Some mercury is released by cremation of human or animal remains. Mercury is used in a variety of industrial applications and manufacturing processes. Increases in power plant emissions and industrial uses over the past 100 years have been accompanied by a three-fold increase in environmentally available mercury. In these forms, mercury remains in the environment indefinitely.

The principal source of human exposure to MeHg is fish consumption. Sea mammals and shellfish also carry variable concentrations of MeHg in their tissues. The predominant source of MeHg in the aquatic environment is atmospheric mercury deposited on the surfaces of bodies of water that is then biomethylated by microorganisms and subsequently biomagnified as it ascends the food chain. Most fish living in US waters have less than 0.5 parts per million (ppm) but some older, larger carnivorous fish at the top of the food chain can contain more than 1 ppm. Tuna, shark, and swordfish all typically exceed 1 ppm. Although the dominant health concerns arise from gestational exposure, infants and children may be exposed postnatally to MeHg from breast milk should their mothers consume foods containing high levels, or if they consume fish or foodstuffs containing fish products.

Developmental Neurotoxicity of Methylmercury

Fishes

During the 1950s outbreaks of MeHg poisoning occurred in several places in Japan. The best know of these took place in Minamata and Niigata. Over 21,000 individuals filed claims with the Japanese government as victims of what became known as Minamata disease; almost 3,000 were certified by the government as actually having the disease (Takizawa & Kitamura, 2001). In Minamata alone, nearly 600 people died. These outbreaks were caused by industrial discharges of mercury into coastal waters or rivers. Fish contaminated by these discharges were subsequently caught and consumed by local residents. Poisoned individuals suffered severe neurological impairments.

Loaves

A later outbreak in Iraq resulted from the consumption of bread made from seed grain coated with a MeHg fungicide (Bakir, et al., 1973). This outbreak affected 6,530 individuals, 439 of whom died. The levels of MeHg documented in the fish in Japan and in the seed grain in Iraq were far higher than those occurring from natural dietary exposure.

Congenital Minamata Disease

In Minamata, Japan, pregnant women who consumed the contaminated fish manifested mild or no symptoms, but gave birth to babies with severe developmental disabilities, including cerebral palsy, mental retardation, and seizures. This outcome, called Congenital Minamata disease, first indicated that the fetal brain may be highly sensitive to MeHg exposure. Following the outbreaks in Minamata and Niigata, 22 cases of Congenital Minamata disease were documented (Harada, 1968). Their level of prenatal exposure to MeHg was never ascertained and no information is available on dose-response relationships in these children.

More Loaves

Investigators from the University of Rochester conducted a limited developmental assessment of the offspring of a total of 83 women who were pregnant during the Iraqi outbreak. Prenatal exposure levels ranged between 1 and 600 ppm as measured in maternal hair growing during pregnancy, an excellent biomarker of exposure. In contrast, MeHg levels seen in fish eaters consuming multiple fish-meals per week rarely exceed 36 ppm in hair (Cernichiari, et al., 1995). The results suggested a dose-response curve associated with delayed milestones that appeared to indicate an adverse effect at exposures as low as 10 to 20 ppm in maternal hair (Cox, 1989). For many years thereafter, these findings were used as a basis for determining the permissible daily intake for methyl mercury exposure (see WHO, 1990). However, the study was not well controlled. Also, the source of exposure in Iraq was not fish consumption and the number of children with neurological findings was small, limiting the generalizability of the results.

More Fishes (and Whales)

In the mid-1980s, two different groups of investigators began two large well-designed and well-executed cohort studies, one in the Republic of Seychelles called the Seychelles Child Development Study (Myers, et al., in press; Davidson, et al., 1998; see Myers and Davidson, 2000 for a review) and the other in the Faeroe Islands (Grandjean, et al., 1997). Both locales are well suited to epidemiological studies, affording many natural controls over confounders, and both populations consume large quantities of seafood. Both studies determined prenatal MeHg exposure and ascertained neurodevelopmental outcomes following delivery. Exposure levels were similar (mean 4.0 ppm in Faeroes and 6.0 in Seychelles). The Seychelles Child Development Study (SCDS) examined their main cohort (n = 779) five times following birth (6.5, 19, 29, 66, and 107 months). The Faeroese cohort was examined at 7 years and again at 14 years.

Reconciling the Differences

The findings from the two studies were different. In the Seychelles, out of a total of 46 primary endpoints measured across five ages, only one endpoint showed a possible adverse association with prenatal MeHg exposure. The Faeroes study reported adverse associations between prenatal MeHg exposure and tests of memory, attention, language, and visual spatial perception measured at seven years of age (Grandjean, et al., 1997). In some cases, these divergent results occurred on identical test measures.

Expert groups have reviewed the Faeroes and Seychelles studies on several occasions (ATSDR, 1999; National Research Council, 2000; NIEHS, 1998). Both the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute of Environmental Health Science (NIEHS) reviews addressed the scientific merit of the studies and concluded that both were methodologically sound and reached scientifically valid conclusions for their respective populations. They concluded that the different results may reflect the differential influences of biological factors not yet identified. The National Research Council (NRC) was charged to "…evaluate the body of evidence that led to the Environmental Protection Agency's (EPA) current RfD [reference dose] for MeHg…and determine whether the critical study, endpoint of toxicity, and uncertainty factors used by EPA in the derivation of the RfD for MeHg are scientifically appropriate" (National Research Council, 2000, p 2.). The NRC report concluded that sufficient evidence was available to concur with EPA's recommendation to lower the RfD from 0.5 to 0.1 μg/kg/day. The data from the Seychelles study were discounted because no significant adverse effects were reported. Subsequently, Later, the Faeroes group reported that the polychlorinated biphenyls (PCBs) present in whale meat and blubber might be confounding the mercury exposure (Grandjean et al., 2001), raising questions about the NRC's conclusions.

Public Policy Issues

There is no doubt that organic mercury is a potent neurotoxicant. Faced with data that point to the increased bioavailability of mercury in the environment, scientists need to inform governments worldwide of the level of exposure that can cause adverse health effects and governments need to develop public health policies that minimize human exposure.

Despite disagreement about the lowest dose at which human health effects may result, some governments have promulgated policies and laws that severely limit or eliminate the use of mercury preservatives in vaccines, and inorganic mercury in dental amalgams. Other governments, including the United States have sought to develop public health strategies that limit human consumption of fish during pregnancy. Unfortunately, the gap between science and policy concerning low-dosage exposure to mercury may not be narrowed for some time. Regulatory bodies in the US such as the EPA and the Food and Drug Administration (FDA), and bodies such as the ATSDR have adopted differing views about appropriate actions to be taken. Regulating the sale of fish high in MeHg or advising pregnant women to refrain from consuming fish high in mercury during their pregnancies may be appropriate provided the agencies can agree on what constitutes a nominally safe dose.

In warning the public about the risks of mercury exposure from consuming fish, we face the alternative risk of frightening consumers into refraining from fish consumption when fish is a primary source of nutrition amongst many groups. Dietary changes that affect essential protein and nutrient intake during pregnancy could prove to be more dangerous to the fetus than the poorly defined risk associated with exposure to MeHg in the fish. Similarly, parents in some parts of the United Kingdom have decided to forego having their children immunized fearing exposure to mercury from the vaccines. Such practices, if they occurred on a large enough scale, could compromise disease control, leading to a greater risk to child health than mercury might present.

Public policies related to regulation of exposure to mercury are thus very complex and are not easily addressed. In a recent comprehensive review of mercury neurotoxicity, Clarkson concluded, "As we…reflect upon the extensive research [on mercury] conducted in our lifetime, we must reluctantly agree with the title of a BBC documentary broadcast over 25 years ago that this metal still remains 'an element of mystery' (2002, p 21). As we decide on such regulatory questions, we must strive to limit the gap between science and policy if we are to choose answers wisely".

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References

ATSDR. *Toxicological profile for mercury: Update*. Atlanta, GA: Agency for Toxic Substances and Disease Registry, 1999.

Bakir F, Damluji DS, Amin-Zaki L, Murtadha M, Khalidi A, Al-Rawi NY, Tikriti S, Dhahir HI, Clarkson TW, Smith JC, Doherty RA. Methylmercury poisoning in Iraq. *Science*, 1973; 181:230-241.

Cernichiari E, Toribara TY, Liang L, Marsh DO, Berlin MW, Myers GJ, Coc C, Shamlaye CF, Choisy O, Davidson P & Clarkson TW. The biological monitoring of mercury in the Seychelles study. *NeuroToxicol*, 1995;16:613-628.

Clarkson TW. The three faces of mercury. *Environ Health Perspect*, 2002;110 (Supplement 1):11-23.

Cox C, Clarkson TW, Marsh DO, Amin-Zaki L, Tikriti S, Myers GJ Dose-response analysis of infants prenatally exposed to methylmercury. An application of a single compartment model to single-strand hair analysis. *Environ Res.* 1989; 31: 640-649.

Davidson P, Myers G, Cox C, Axtell C, Shamlaye C, Sloane-Reeves J, Cernichiari E, Needham L, Choi A, Wang Y, Berlin M, Clarkson TW. Effects of prenatal and postnatal methylmercury exposure from fish consumption at 66 months of age: the Seychelles Child Development Study. *JAMA* 1998; 280:665-676.

Fitzgerald W, Clarkson T. Mercury and monomethylmercury: present and future concerns. Environ Health Perspect 1991;96:159-166.

Grandjean P, Weihe P, Burse VW, Needham LL, Storr-Hansen E, Heinzow B, Debes F, Murata K, Simonsen H, Ellefsen P, Budtz-Jorgensen E, Keiding N, White RF. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicol Teratol,* 2001;23:305-317.

Grandjean P, Weihe P, White RF, Debes F, Araki S, Yokoyama K, Murata K, Sorensen N, Dahl R, Jorgensen PJ. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol,* 1997*;*19: 417-428.

Harada Y. Congenital (or fetal) Minamata disease. In *Minamata Disease*. Study group of Minamata Disease (Eds). Japan: Kumamoto University, 1968 pp 93-118.

Mason R, Fitzgerald W, Morgan F. Gecehemico Cosmochinm Acta, 1994;58(15):3191-3194.

McKeown-Eyssen G., Reudy J, Neims A. Methylmercury exposures in Northern Quebec, II: Neurologic findings in children. *Am J Epidemiol*. 1983; 118, 470-479.

Myers GJ, Davidson PW. Twenty-seven years studying the human neurotoxicity of methylmercury exposure. *Environ Res* 2000:83;275-285.

Myers G, Davidson P, Cox C, Shamlaye C, Palumbo D, Cernichiari E, Sloane-Reeves J, Wilding J, Kost J, Huang L-S, Clarkson TW. Prenatal methylmercury exposure from fish consumption: associations at 9 years of age in the Seychelles Child Development Study. *Lancet*, in press.

NIEHS. *Workshop on Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury*. Bethesda, MD: National Institutes of Health, 1998.

National Research Council. *Toxicological effects of methylmercury*. Washington, DC: National Academy Press, 2000.

Takizawa Y, Kitamura S. Estimation of the incidence of mercury exposure in the Minamata and Niigata areas usinmg mathematical model from Iraqi poisoning. In Y. Takizawa & M. Osame (eds). *Understanding Minamata Disease: Methylmercury Poisoning in Minamata and Niigata Japan*. Tokyo: Japan Public Health Association, 2001, pp. 27-32.

WHO. Methylmercury. Environmental Health Criteria.101. Geneva: World Health Organization, 1990.